

Appl. No. : 10/002,796
Filed : November 15, 2001

REMARKS

Claims 40-47 and 50-52 remain pending in the present application. Applicants respond below to the specific rejections raised by the Examiner in the final Office Action mailed May 6, 2005, which are maintained in the Advisory Action. For the reasons set forth below, Applicants respectfully traverse.

Rejection Under 35 U.S.C. § 101 – Utility

In the final Office Action, the Examiner maintained the rejection of Claims 40-47 and 50-52 as lacking a specific, substantial, and credible utility for the reasons set forth in the Office Actions mailed April 27, 2004 and August 24, 2004. The Examiner stated that the asserted utilities for the PRO444 polypeptides, namely use as diagnostic markers for pericyte-associated tumors, use as reagents to identify and isolate PRO444 antagonists, and use as therapeutics to stimulate angiogenesis, were unpersuasive. The Examiner alleged that there is no evidence that PRO444 is exclusively present or expressed at altered levels in pericyte-associated tumors, and hence PRO444 cannot be used as a marker for the same. The Examiner also argued that there is no evidence that PRO444-induced activation of *c-fos* is specifically related to pericyte-associated tumors or angiogenesis.

The Examiner maintained that Dr. Gerritsen's Declaration, submitted with Applicants' Request for Continued Examination filed Jan 21, 2005, is insufficient to overcome the rejection under 35 U.S.C. § 101. Specifically, the Examiner asserted that Dr. Gerritsen's declaration is not backed by scientific literature showing the importance of pericytes in regulating angiogenesis or the role of *c-fos* in regulating cancer and angiogenesis. Office Action at 4. The Examiner maintained that, as Dr. Gerritsen testifies, many growth factors are known to induce *c-fos* in pericytes. Office Action at 5. The Examiner cited Sakurai et al. and Otani et al. as supporting evidence of the various known regulators of *c-fos*. The Examiner concluded that since PRO444 is not the only regulator of *c-fos* there is thus "no specific biological function that could be particularly attributed to PRO444 with respect to its ability to activate *c-fos* expression in pericytes." Office Action at 5. The Examiner also cited to Ozerdem et al. for the proposition that the role of pericytes in the formation of tumor neovasculature varies depending on the type of tissue and tumor, and concluded that PRO444 cannot be specifically associated with the onset of cancer and angiogenesis. Finally, the Examiner argued that Coulon et al. demonstrates that

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demonstrates that *c-fos* is activated in a range of different cell types, and therefore activation of *c-fos* in pericytes is not specific.

Applicants respectfully disagree.

Utility – Legal Standard

According to the Utility Examination Guidelines (“Utility Guidelines”), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted “specific, substantial, and credible utility” or a “well-established utility.”

Under the Utility Guidelines, a utility is “specific” when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of “substantial utility” defines a “real world” use, and derives from the Supreme Court’s holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that “The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility.” In explaining the “substantial utility” standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a ‘substantial’ utility.” (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that “Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.” Further, “to violate § 101 the claimed device must be totally incapable of achieving a useful result.” *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), citing *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

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Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: “If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that “to overcome the presumption of truth that an assertion of utility by the applicant enjoys” the PTO must establish that it is “more likely than not that one of ordinary skill in the art would doubt (i.e., ‘question’) the truth of the statement of utility.” M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.** M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, “unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.” *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or “more likely than not” standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

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[T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true “beyond a reasonable doubt.” **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence “that one of ordinary skill in the art would reasonably doubt the asserted utility.” *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

[T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be “*reasonably* indicative of the desired [pharmacological] response.” In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior.” *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art “to a reasonable probability.” In addition, the evidence need not be direct, so long as there is a “sufficient correlation” between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds.

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Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

[I]n *vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is “an invariable exact correlation” between gene expression and protein expression. Instead, Applicants’ position detailed below is that a measured change in gene expression in cancer cells establishes a “significant probability” that the expression of the encoded polypeptide in cancer will also be changed based on “a reasonable correlation therebetween.”

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.** The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful for the treatment of tumors and for the stimulation of angiogenesis.

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In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert they have provided reliable evidence that PRO444 stimulates *c-fos* in pericytes. As discussed below, at the time the application was filed, pericytes were known to have a role in angiogenesis. Specifically, pericytes were known to be involved in survival of newly formed vasculature, for example by secretion of VEGF. Further, as shown below, it was well known at the time the application was filed, that VEGF is a potent angiogenic factor, and the VEGF expression is regulated by *c-fos*. Accordingly, more likely than not, the skilled artisan would believe that PRO444, as a stimulator of *c-fos* in pericytes, would be useful as a therapeutic target for pathological angiogenesis, as well as a tool for stimulating angiogenesis.

Applicants understand the Examiner to be making the following arguments in response to Applicants' asserted utilities:

1. The Examiner argues that there is no evidence that PRO444 *c-fos* induction in pericytes is specifically related to cancer or angiogenesis. Office Action at 4.
2. Citing Otani et al., Sakurai et al. and Coulon et al., the Examiner argues that several growth factors are capable of inducing *c-fos* expression, and therefore PRO444-induced *c-fos* induction is not a biological activity that can be particularly attributed to PRO444.
3. Citing Ozerdem et al., the Examiner argues that the role of pericytes in angiogenesis is not fully understood, and therefore induction of *c-fos* cannot be specifically associated with cancer or angiogenesis.
4. The Examiner argues that there is no evidence that PRO444 is present exclusively or expressed at altered levels in pericyte-associated tumors.
5. The Examiner argues that the Declaration of Dr. Gerritsen represents only Dr. Gerritsen's conclusions, and lacks references to scientific publications, and therefore is unpersuasive.

Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Further, Applicants submit that *even if* the PTO met its initial burden, Applicants have provided rebuttal evidence establishing that more likely than not that a person of skill in the art would be convinced, to a reasonable probability,

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that the asserted utility of PRO444 as a target for tumor therapy, and as a stimulator of angiogenesis, is true.

As discussed in detail below, contrary to the Examiner's assertion, the art at the time of filing demonstrated that pericytes are involved in angiogenesis, and that VEGF was important in angiogenesis. Specifically, the references cited below demonstrate that VEGF functions as a potent angiogenic factor, and is closely involved in tumorigenesis due to its mitogenic stimulation of endothelial cells (EC's), as well as functioning as a survival factor for newly formed vessels. The references at the time of filing also established that VEGF expression is regulated by *c-fos*.

Finally, Applicants submit that the evidence offered by the Examiner in support of the rejection of Applicants' asserted utilities demonstrates *c-fos* induction in pericytes is involved in angiogenesis, and illustrates the soundness of Applicants' asserted utilities.

Pericytes have an established role in angiogenesis

Applicants submit herewith references illustrating the state of the art regarding pericyte control of angiogenesis at the time the application was filed. Nehls et al. (1992) *Cell Tissue Res.* 270:469-474 describes pericyte involvement in capillary sprouting during angiogenesis *in situ*. The authors induced angiogenesis in mouse mesentery tissue and used immunofluorescence to identify pericytes. The authors found that pericytes were regularly positioned at and in front of the advancing tips of endothelial sprouts, and bridging gaps between the leading edges of endothelial sprouts. The authors concluded that pericytes are involved in capillary sprouting. Rhodin et al., (1989), *J. Submicrosc. Cytol. Pathol.* 21:1-34 also found that pericytes were regularly found in association with most capillary sprouts examined. Rhodin, at 12. The role of pericytes in angiogenesis is also described in Ozerdem, cited by the Examiner. Specifically, Ozerdem's study confirmed previous studies showing that pericytes contribute to angiogenic sprout formation in neoplastic neovascularization. Due to their role in angiogenesis, Ozerdem suggests that "pericytes represent a target for treatment to up-regulate or down-regulate vascularization," for example in cancer. Ozerdem, at 248.

As discussed in further detail below, VEGF is a well-known and well-characterized potent angiogenic factor, and its role in pathological angiogenesis was well-documented at the time of filing of the application. Studies had shown that VEGF is involved in survival of

endothelial cells in newly formed vessels. Alon et al., (1995), *Nat. Med.* 1(10):1024-1028, examined the role of VEGF in retinopathy of prematurity (ROP), a disorder that ultimately results in blindness. It was generally accepted at the time that VEGF caused the abnormal vasoproliferation in ROP. Alon showed that the absence of VEGF during the early stage in ROP resulted in blood vessel regression. Exogenously added VEGF reversed this process. Thus, Alon concluded that VEGF is involved in survival of newly formed vasculature. The studies of Benjamin et al. (1997), *Proc. Nat. Acad. USA* 94:8761-8766, demonstrated this same phenomenon. Briefly, Benjamin showed that shutting off VEGF expression in tumors resulted in regression of preformed tumor vessels. Notably, Benjamin commented that this finding was "critical in the success of many angiogenic and anti-angiogenic therapies." Benjamin at 8675. See also Fidler et al., (2000), *Cancer J.* 6(Suppl. 3) S225-236, for a discussion of the role of VEGF in survival of newly formed vasculature.

A review by Ellis et al. describes the role of pericytes in angiogenesis as it relates to tumor biology. Ellis, (2002), *Oncology* 16(5):14-22. Ellis explains that "the tumor microenvironment is a caustic one. . .[t]herefore, for these fragile endothelial cells [that represent the new primitive capillary network] to survive, they must be exposed to endothelial cell survival factors. . .Endothelial cell survival factors include pericytes that may stabilize endothelium. . .by secretion of endothelial cell survival factors such as VEGF." Ellis, at 20. Thus, it was known that one of the roles in angiogenesis that pericytes plays is to promote survival of newly formed vasculature, by secreting VEGF.

The references cited above provide the evidentiary support from the scientific literature for Dr. Gerritsen's testimony that "pericytes help. . .stabilize newly formed blood vessels" (Gerritsen Decl., ¶6), and illustrate that Dr. Gerritsen's testimony is backed by scientific literature. At the time the Application was filed, those skilled in the art appreciated that pericyte cells were involved in angiogenesis, and that the expression of VEGF by pericyte cells was involved in survival of newly formed vasculature.

VEGF has an established role in angiogenesis

Applicants submit that at the time the Application was filed, VEGF was widely-recognized as an angiogenic factor, playing a central role in pathogenic angiogenesis. Applicants

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submit herewith and discuss below references that demonstrate the state of the art at the time the application was filed regarding VEGF biology.

VEGF is a potent mitogen and a chemoattractant for endothelial cells (EC's). In addition VEGF promotes vascular permeability for EC's. Ferrara, N., (1995), *Breast Cancer Res.* 36:127-137, 127. Early studies demonstrated that VEGF promotes angiogenesis *in vitro*, by inducing confluent microvascular endothelial cells to invade a collagen gel and form tube-like structures. See, e.g., Pepper, M., et al. (1992), *Biochem. Biophys. Res. Comm.* 189:824-831. Augmented VEGF expression was known to be correlated with vascularization associated with increased tumor growth. (See, Benjamin et al., at 8671, and references cited therein). Inhibition of VEGF production or function was also shown to lead to inhibition of tumor growth. *Id.*, and references cited therein. This activity, in combination with VEGF's known function in mediating endothelial cell survival in newly formed vasculature, discussed above, led to the characterization of VEGF as "the pivotal *in vivo* mediator of . . . pathophysiological angiogenesis." Kolch et al., (1995) *Breast Cancer Res. Treat.* 36:139-155, at 139.

Applicants submit that the references cited above demonstrate that at the time the Application was filed, those skilled in the art appreciated the critical role of VEGF in angiogenesis, as required for neovascularization, survival of newly formed vasculature, and vascular permeability.

c-fos stimulates VEGF expression

As described in Janknecht, cited by the Examiner, *c-fos* encodes a subunit of the nuclear transcription factor AP-1. At the time the application was filed, *c-fos* was a widely-recognized proto-oncogene known to regulate cellular proliferation and differentiation. Janknecht at 443. At the time of filing of the instant application it was accepted by those skilled in the art that AP-1 played an important role in the expression of VEGF.

In 1990, Tishcer et al. analyzed the human gene for VEGF. Tischer et al. (1991), *J. Biol. Chem.* 266(18):11947-11954. The authors found that the promoter region for hVEGF contains several AP-1 binding sites, suggesting that *c-fos* is a regulator of VEGF expression. Tischer at 11953. Similarly, the structure of the mouse VEGF gene revealed "multiple consensus binding sties for AP-1." Shima, et al., (1996) *J. Biol. Chem.* 271(7):3877-3882, 3882. Further, in Kolch's review "Regulation of the expression of the VEGF/VPS and its receptors: role in tumor

angiogenesis," Kolch summarizes the state of the art at the time by noting "[a]t present, a comprehensive assessment of several studies highlights the AP-1 transcription factor as an important common denominator for the regulation of VEGF expression." Kolch, at 144. Kolch highlights various pathways in which both *c-fos* and VEGF expression are regulated, including through the Ras and Raf pathways. *Id.* at 144-145. Kolch also links the induction of *c-fos* expression through the Raf and Ras pathways with conversion to a tumorigenic phenotype through activation of VEGF. *Id.*, at 145.

Applicants submit that the references discussed above demonstrate that at the time the instant application was filed, those skilled in the art appreciated the role of *c-fos* in VEGF expression, and hence, the role of *c-fos* in the angiogenic process, including neovascularization and stabilization of newly formed vasculature.

The skilled artisan would believe that indirect regulators of angiogenic factors (VEGF, IL-8) are useful as therapeutic targets for cancer therapy

As Dr. Gerritsen testified, Applicants submit that "a skilled artisan would reasonably conclude that neutralizing compounds capable of stimulating *c-fos* expression in pericytes (*e.g.*, PRO444) could be useful in preventing the onset and/or progression of cancer and/or angiogenesis." Gerritsen Decl., ¶6. The discussion above demonstrates that at the time of filing of the instant application, those skilled in the art appreciated the role of pericytes in capillary sprout formation and the survival of neovasculature. Further, the art at the time demonstrated that VEGF was expressed in pericytes, and that VEGF is involved in both proliferation of EC cells and in survival of newly formed vasculature. Finally, those skilled in the art appreciated the central role of *c-fos* in VEGF expression. Thus, Applicants submit, and as Dr. Gerritsen testified, a skilled artisan would reasonably conclude that neutralizing compounds capable of stimulating *c-fos* expression in pericytes would be useful in tumor therapy.

As proof of this principle, in a review entitled "Angiogenesis inhibitors in Oncology," Ellis states that antiangiogenic strategies involved, among others, strategies that decrease the activity of specific angiogenic factors (such as VEGF), and strategies that indirectly downregulate activity of angiogenic and survival factors. Ellis et al., (2002) *Oncology* 16(5):14-22. Ellis proposes that "[s]trategies that downregulate the upstream signaling pathways to VEGF and other angiogenic factors may indirectly downregulate VEGF activity and angiogenesis."

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Ellis, at 20. Applicants submit that Ellis' discussion of various strategies for cancer therapy describes identification of compounds such as PRO444, that act indirectly to regulate the activity of angiogenic and survival factors, such as VEGF, demonstrating that those skilled in the art believe that compounds such as PRO444 are useful in cancer therapy.

Applicants note that the first strategy proposed by Ellis has been demonstrated to be effective. A VEGF-specific antibody, bevacizumab, has been successfully used to treat several cancer types. See, Kirkpatrick, P., (2005), *Nat. Rev. Drug Disc.* S8-S9. Willett et al. report that bevacizumab has antivasular effects in human rectal cancer. Willett et al. (2004) *Nature Medicine*, 10(2):145-147.

In summary, Ellis' discussion provides support for Dr. Gerristen's testimony that those skilled in the art would more likely than not believe that factors that induce the expression of *c-fos*, a known upstream regulator of VEGF, are useful targets for tumor therapy.

c-fos activation in pericytes has a specific activity associated with angiogenesis

Applicants next address the Examiner's arguments that since many factors are known to stimulate *c-fos*, there can be no specific function attributable to PRO444 induction of *c-fos* in pericytes. As an initial matter, Applicants submit that Coulon et al. does not discuss *c-fos* activation in pericytes, and is thus not relevant to Applicants' asserted utility. Sakurai et al. and Otani et al. both address *c-fos* activation in pericyte cells and are discussed below.

As correctly stated by the Examiner, Sakurai et al. and Otani et al., show that *c-fos* activation in pericytes can be achieved through prostaglandins and angiotensin II, respectively. The Examiner argues that these findings demonstrate that no function can be attributed to PRO444 with respect to its ability to activate *c-fos* in pericytes, because "many growth factors are capable to stimulate growth of pericytes through activation of [the] *c-fos* pathway." Office Action mailed May 5, 2005, at 5.

Applicants submit that activation of *c-fos* in pericytes by prostaglandins, angiotensin II, and VEGF all lead to angiogenesis, and have all been implicated in pathological angiogenesis. Sakurai, cited by the Examiner, examined the role of prostaglandins in proliferative retinopathy, in which "the underlying mechanism. . . is the formation of new vessels." Sakurai, at 2774. The authors hypothesized that prostaglandins, well-known inflammatory mediators, may play a role in the development of new vessels. *Id.* Pericytes treated with prostaglandins induced *c-fos*

expression, and as anticipated, also showed increased levels of VEGF expression, "a key growth factor in neovascularization." *Id.* The authors conclude that their findings provide an explanation "for the known link between angiogenesis and chronic inflammation," *Id.* at 2780. Thus, contrary to the Examiner's position, Sakurai demonstrates that factors that stimulate *c-fos* in pericytes lead to stimulation of VEGF, and angiogenesis.

The second reference that the Examiner cites which relates to *c-fos* activation in pericytes is Otani et al. Otani et al. observed that angiotensin II and VEGF activate *c-fos* in pericytes. These data are fully consistent with Applicants' assertion that *c-fos* activation in pericytes, *e.g.*, by PRO444, angiotensin II, or VEGF, leads to a specific biological activity -- angiogenesis. Otani examined the role of angiotensin II in retinal pericytes. The authors found the angiotensin II induced VEGF expression in bovine pericytes, through the *c-fos* pathway. The authors also found that VEGF released by the pericytes stimulated retinal endothelial growth, and summarized their findings by stating that "[t]hese findings suggest that AII might induce angiogenic activity through a paracrine function of VEGF in retinal microvascular cells." Otani, at 1192. Thus, the authors found that *c-fos* indirectly induced angiogenesis through VEGF.

As shown above, the references relied upon the Examiner as supporting the position that no specific activity can be attributed to PRO444, since other factors are known to stimulate *c-fos* in pericytes, actually fully support Applicants' position. In particular, in both references which disclose *c-fos* activation in pericytes, the authors discovered that *c-fos* induction led to VEGF induction, which led to angiogenesis. Therefore, the references cited by the Examiner demonstrate that those skilled in the art would more likely than not believe that PRO444, as an inducer of *c-fos* in pericytes, would promote angiogenesis, and as such is a useful therapeutic target for pathological angiogenesis.

Conclusion

Applicants submit that the evidence submitted herewith establishes that factors capable of inducing *c-fos* in pericyte cells are useful tools for stimulating angiogenesis and as useful tools to design anti-angiogenic therapeutics, for example for tumor therapy. First, Applicants demonstrated that at the time the application was filed, the role of pericytes in angiogenesis – specifically capillary sprout formation and survival of neovasculature - had been established. Applicants also presented evidence that the role of VEGF as a potent angiogenic factor and as a

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survival factor for newly formed vasculature was established. Further, Applicants also presented evidence that it was known that *c-fos* played a central role in VEGF expression. Taken together, the above evidence establishes that more likely than not, one skilled in the art would have believed Applicants' asserted utilities for PRO444 at the time of filing of the application. As proof of this, Applicants provided evidence that those skilled in the art had postulated that upstream regulators of VEGF are useful targets tumor therapy, demonstrating that those skilled in the art would believe PRO444, as an upstream regulator of VEGF in pericytes, is useful for angiogenic and anti-angiogenic therapies, such as tumor therapy. Finally, Applicants have shown that the evidence presented by the Examiner regarding *c-fos* activation in pericytes, rather than establishing that PRO444 lacks specific and substantial utility, clearly demonstrates that those skilled in the art accept the theory upon which Applicants' asserted utility rests, *i.e.*, that stimulation of *c-fos* in pericyte cells leads to angiogenesis.

Applicants submit that it is more likely than not that one skilled in the art would believe Applicants' asserted utility for PRO444. Applicants respectfully request that the Examiner withdraw the rejection of Claims 40-47 and 50-52 under 35 U.S.C. § 101.

Rejection Under 35 U.S.C. § 112, First Paragraph – Enablement

The Examiner has maintained the rejection of Claims 40-47, and 50-52 as not being enabled since the claimed invention is allegedly not supported by either a specific and substantial asserted utility, or a well-established utility.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. Applicants therefore request that the Examiner reconsider and withdraw the enablement rejection to the extent that it is based on a lack of utility for the claimed polypeptides.

Rejection Under 35 U.S.C. § 112, First Paragraph – Written Description

The Examiner has maintained the rejection of Claims 40-44 under 35 U.S.C. § 112, first paragraph, as lacking adequate written description. The Examiner asserts that the specification fails to provide written description for the claimed variants of SEQ ID NO:8, and that while a skilled artisan could determine if a polypeptide induces *c-fos* activation in pericytes, this

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limitation does not satisfy the written description requirement. The Examiner asserts that the statement that a compound is part of the invention and a reference to a potential method of isolating it is not sufficient, and that the compound itself is required.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure “reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter.” *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant’s disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

Applicants submit that the pending claims relating to polypeptides having 80% to 99% sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO: 9 with the functional recitation “wherein said isolated polypeptide induces *c-fos* expression” are also adequately described. In Example 14 of the written description training materials, the written description requirement was found to be satisfied for claims relating to polypeptides having 95%

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homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same activity *in vivo*. In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make polypeptides which have at least 80% sequence identity to SEQ ID NO: 9, and the specification discloses how to test to determine if the polypeptides induce *c-fos* expression. The facts at hand are indistinguishable from those set forth in Example 14. Like Example 14, the genus of polypeptides that have at least 80% or 99% sequence identity to the disclosed amino acid sequences will not have substantial variation since all of the variants must have the same ability to induce *c-fos*.

Furthermore, while Applicants appreciate that actions taken by the PTO in other applications are not binding with respect to the examination of the present application, Applicants note that the PTO has issued many patents containing claims to variant nucleic acids or variant proteins where the applicants did not actually make such nucleic acids or proteins. Representative patents include U.S. Patent No. 6,737,522, U.S. Patent No. 6,395,306, U.S. Patent No. 6,025,156, U.S. Patent No. 6,645,499, U.S. Patent No. 6,498,235, and U.S. Patent No. 6,730,502, which are attached hereto as Exhibits 1-6.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO: 9, and by describing the *c-fos* induction assay, which results in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

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Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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